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ORIGINAL ARTICLE

Novel oral iron therapy for iron deficiency anaemia: How to value safety in a new drug?

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Aims: Novel oral iron supplements may be associated with a reduced incidence of adverse drug reactions compared to standard treatments of iron deficiency anaemia. The aim was to establish their value-based price under conditions of uncertainty surrounding their tolerability.

Methods: A discrete-time Markov model was developed to assess the value-based price of oral iron preparations based on their incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS in the UK. Primary and secondary care resource use and health state occupancy probabilities were estimated from routine electronic health records; and unit costs and health state utilities were derived from published sources. Patients were pre-menopausal women with iron deficiency anaemia who were prescribed oral iron supplementation between 2000 and 2014.

Results: The model reflecting current use of iron salts yielded a mean total cost to the NHS of £779, and 0.84 QALYs over 12 months. If a new iron preparation were to reduce the risk of adverse drug reactions by 30–40%, then its value-based price, based on a threshold of £20 000 per QALY, would be in the region of £10–£13 per month, or about 7–9 times the average price of basic iron salts.

Conclusions: There are no adequate, direct comparisons of new oral iron supplements to ferrous iron salts, and therefore other approaches are needed to assess their value. Our modelling shows that they are potentially cost-effective at prices that are an order of magnitude higher than existing iron salts.

KEYWORDS
cost and cost analysis, cost-effectiveness, iron, iron-deficiency anaemia

1 | INTRODUCTION

Iron deficiency is the most common cause of anaemia worldwide[1,2] and, for uncomplicated cases, it is treated with oral iron supplementation. In England, 7.98 million prescriptions for oral iron were dispensed in the community in 2018, and >99% of these were in the form of simple iron salts, typically sulfate, gluconate or fumarate.[3] These are effective and inexpensive (£1.38 per 28 tablets) but adverse drug reactions (ADRs) occur in about a third of patients. Common ADRs are gastrointestinal and include nausea, vomiting and constipation,[4] and these lead to frequent dose adjustments, change in prescription, non-adherence or treatment discontinuation. As a result,

the true cost of prescribing "inexpensive" iron salts may be significantly higher than the cost of the product itself, owing to associated increases in the utilisation of health care services. In turn, this has prompted the development of novel oral iron forms that seek to reduce ADRs or a switch away from oral iron to intravenous strategies.[5,6] Both alternative approaches are markedly more expensive than oral iron salts but the key issue concerns the pricing at which they would become cost-effective.

A meta-analysis of 20 randomised controlled trials identified a relative risk of 1.59 (95% confidence interval [CI] 1.43–1.76) for gastrointestinal ADRs to ferrous sulfate versus placebo.[4] Therefore, given that approximately one third of patients taking oral iron experience ADRs (29.9% for ferrous gluconate, 30.2% for ferrous sulfate and 43.4% for ferrous fumarate),[7] an absolute ~12% of all patients prescribed common iron salts might avoid gastrointestinal ADRs if an ideal treatment were available. Indeed, quite a number of alternative iron preparations, either on the market or in the pipeline, claim to have superiority over ferrous iron salts in terms of acute, gastrointestinal ADRs. Gastrointestinal intolerance is generally considered to relate to the oxidation of ferrous iron in the gut lumen following iron ingestion, and the generation of damaging reactive oxygen species. To avoid this, iron may be chelated, potentially in its ferrous form (e.g., iron bis-glycinate[8]) or, most commonly, as ferric iron (e.g., ferric maltol, ferric citrate, ferric EDTA[9,10]). This not only helps to maintain iron in a soluble form but also opposes the drive for iron redox cycling in the intestine. An alternative approach involves oral delivery of iron as a nanoparticle (e.g., iron hydroxide adipate tartrate[11]) which also prevents luminal redox activity and delivers a bolus dose to the enterocyte lysosome, which is a safe house for iron dissolution, recycling and systemic absorption. Finally, an approach that is a hybrid of the two mechanisms described above has also been proposed with sucrosomial iron, which consists of ferric pyrophosphate coated with a lecithin and sucrose esters. This is absorbed as sucrose ester conjugates and particles or vesicle-like structures.[9] With all these potential therapeutic options, decision-making for the prescriber is clearly challenging.

A key determinant for informing decisions concerning the prescribing of medicines is their cost-effectiveness. The National Health Services (NHS) in the UK operate a threshold in the range of £20 000 to £30 000 per quality-adjusted life year (QALY) gained, below which medicines are considered to represent good value for money.[12] It follows that the value-based price of new medicines may be established from knowing the health gains—such as reduction in ADRs—that can be achieved. A medicine priced up to its value-based price would consequently be cost-effective.[13]

The aim of this study was to estimate the value-based price, centred on the cost per QALY as a measure of value to the NHS, of oral iron therapies seeking to replace simple oral iron salts.

What is already known about this subject

- Novel oral iron supplements may be associated with a reduced incidence of adverse gastrointestinal reactions but they might not be cost-effective compared with inexpensive iron salts.

What this study adds

- This analysis provides a framework for setting prices according to incidence of adverse drug reactions, and suggests that novel oral iron supplements could be cost-effective at prices that are several-fold higher than existing oral iron salts.
- Estimates of the value-based prices of drugs in development provide a basis for assessing commercial viability, while also assisting the healthcare payers in their horizon scanning activities.

2 | METHODS

A cost-utility analysis was performed from the perspective of the NHS in the UK to estimate the value-based price of a hypothetical new iron therapy as an alternative to inexpensive ferrous iron salts for the management of iron deficiency anaemia in adult patients. A decision analytic model was developed, with probabilities of transitioning among six health states relevant to the management of iron deficiency anaemia based on data obtained from the Clinical Practice Research Datalink (CPRD); utilities based on EuroQol (EQ)-5D-3L tariff scores; and direct medical costs of primary and secondary care services based on CPRD and linked Hospital Episode Statistics (HES) data. The health economic analysis was conducted over a 12-month time horizon. The model had a cycle length of 60 days and a half cycle correction was applied.

2.1 | CPRD and HES data

The analysis used the CPRD-GOLD database of anonymised, longitudinal, primary care clinical data contributed by general practices from across the UK. CPRD had a coverage of over 11.3 million patients from 674 practices in the UK in 2013, and has been validated to be representative of the UK population for age, sex and ethnicity.[14] The CPRD allows access to linked HES data from NHS Digital. This administrative dataset records all NHS England hospital inpatient admissions, including combined day case and ordinary elective spells.

The protocol for this study (reference number 14_201) was approved scientifically and ethically by the CPRD Independent Scientific Advisory Committee.

2.2 | Study population and treatments

The CPRD was accessed to identify female patients, aged between 18 and 45 years (i.e., typically pre-menopausal) who were prescribed,

between January 2000 and October 2014, at least one of the top six iron products (which were all ferrous salts) by dispensing volume from the prescription cost analysis database.[15] The product codes for these in CPRD are: dried ferrous sulfate tablets 200 mg (33); ferrous fumarate tablets 210 mg (3035); ferrous gluconate tablets 300 mg (712); ferrous fumarate tablets 322 mg (2915, 3151); ferrous fumarate capsules 305 mg (5045, 6052); and dried ferrous sulfate MR tablets 325 mg (1745, 5582). A course of treatment was defined by a new prescription of oral iron distinct from the immediate previous oral iron prescription (by type or by dose), or a prescription of the same oral iron dated more than 2 months after the previous prescription date.

2.3 | Health states

CPRD and HES data were used to estimate the probabilities of patients residing in each of six mutually exclusive health states, defined by their response and tolerance to treatment (Table 1). The following health states regarding anaemia improvement at assessments (haemoglobin test taken or hospitalisation) within a course of treatment were defined: no improvement of haemoglobin with/without treatment tolerance (States 1 and 3); improvement of haemoglobin with/without treatment tolerance (States 2 and 4); hospital referral (State 5); anaemia resolved (State 6). Further definitions of haemoglobin improvement are provided in the Appendix in the Supporting Information.

Patients were considered intolerant of iron supplementation if their primary or secondary medical records indicated treatment cessation coinciding with a potential ADR (using Read codes for symptoms such as constipation, diarrhoea, nausea, heartburn), a reduction in daily dose or a change in product class. Treatment intolerance was ascertained for each course of treatment and was therefore time-invariant within a given course of treatment.

2.4 | Transition probabilities

A previously described discrete-time Markov model with multinomial logistic regression was used to estimate transition probabilities between health states[16] (see Appendix in the Supporting Information). This was simplified for the economic analysis by averaging the probabilities across doses and treatment courses to provide a single matrix of time-dependent state occupancy probabilities (Table 1). The Markov model is depicted schematically in Figure 1.

2.5 | Health state utilities

Health state utilities were derived from a purposive review of the literature (see Appendix in the Supporting Information).

For the "*no improvement & tolerant*" health state, utilities were assumed to be represented by data from a study of iron treatment for a population of 236 women with heavy menstrual bleeding (mean baseline Hb 11.0 g/dL).[17] This study reported a mean baseline EQ-5D utility score of 0.76. In the absence of any specific evidence, this utility value was also applied to the "*improvement & intolerant*" health state, on the assumption that the health effects of an improvement in iron deficiency is offset by the adverse reaction to the iron supplementation.

Peuranpää et al.[17] reported an improvement in Hb at 12 months of 1.2 g/dL following iron supplement intake. The corresponding utility (0.85) was assumed for the "*improvement & tolerant*" health state.

The disutility associated with being treatment-intolerant was determined from a trial of adult patients with iron-deficiency anaemia and who had failed, or were intolerant to, oral iron therapy.[18] Summary responses to the SF-36 were converted to EQ-5D-3L utilities,[19] which necessitated data to be extracted by digitising figures using WebPlotDigitizer.[20] The difference in EQ-5D-3L utility of 0.04 between baseline (mean Hb of 8.9 g/dL) and the end of follow-up (mean Hb of 11.7 g/dL), was subtracted from 0.76 to estimate the utility of the "*no improvement & intolerant*" health state, as 0.72.

For the "*hospital state*" utility value, International Classification of Diseases (ICD)-10 codes obtained from HES data were converted to ICD-9 in order to estimate the marginal disutility.[21] This was based on UK preference scores applied to EQ-5D descriptive questionnaire responses in relation to 135 chronic, ICD-9 coded conditions in the US-based Medical Expenditure Panel Survey, and controlled for gender, age and ethnicity. The mean disutility score for iron deficiency anaemia of −0.036 was subtracted from the "*no improvement & tolerant*" health state utility score, resulting in a mean utility score for the "*hospital state*" of 0.72.

TABLE 1 Time-dependent health state probabilities

Time since start of treatment	State 1 No improvement & tolerant	State 2 Improvement & tolerant	State 3 No improvement & intolerant	State 4 Improvement & intolerant	State 5 Hospitalisation	State 6 Anaemia resolved
60 days	0.1880	0.1572	0.3239	0.0518	0.0045	0.2746
120 days	0.0958	0.1426	0.2277	0.0631	0.0230	0.4476
180 days	0.0600	0.1145	0.1718	0.0630	0.0295	0.5612
240 days	0.0427	0.0916	0.1365	0.0590	0.0293	0.6408
300 days	0.0327	0.0745	0.1126	0.0540	0.0266	0.6996
360 days	0.0261	0.0615	0.0954	0.0489	0.0235	0.7445
420 days	0.0214	0.0515	0.0825	0.0442	0.0206	0.7798

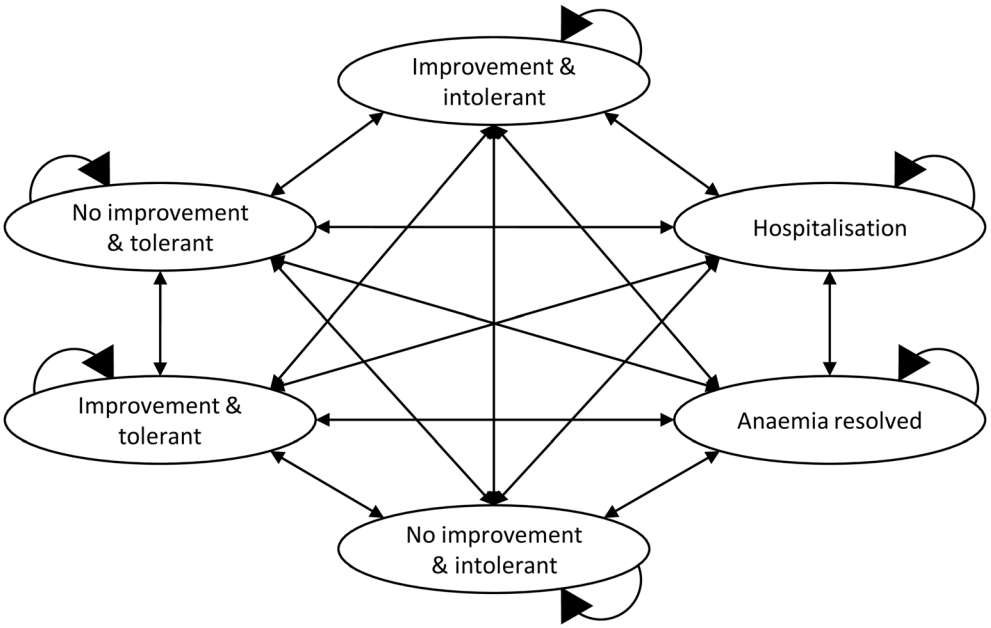


FIGURE 1 Schematic depiction of the economic model, indicating each mutually exclusive health state, and with transition probabilities represented by arrows

The health utility for the state of "*anaemia resolved*" was based on UK population norms.[22] A utility score of 0.90 was calculated from the mean of utility scores of 0.93, 0.91 and 0.85 reported for women in the age categories of 25–34, 35–44 and 45–54 years, respectively.

2.6 | Resource use and costs

CPRD data were used to identify patients' prescribed iron supplementation, blood tests and visits to the general practitioner (GP). Linked HES data were available for 139 069 patients of the sample of 254 262 patients. These were filtered to include only observations that occurred in one health state at any one time, resulting in 30 541 participants. HES data were used to identify inpatient and outpatient hospital attendances.

The unit costs of medicines were sourced from the British National Formulary (BNF),[23] and the total cost calculated by multiplying the cost for the daily quantity of iron supplement by the number of days of treatment per patient.

The cost of a haemoglobin test (£3.37) was obtained from the National Schedule of Reference costs 2015–16 (phlebotomy Healthcare Resource Group [HRG] code DAPS08), while GP consultations were costed at £45, based on an average of 11.7 minutes per consultation[24] (Table 2).

Patients who had hospital care (as inpatient stays or outpatient visits), which occurred within the period they were treated for iron deficiency, were attributed HRG codes. HRG codes define patients' episodes of consultant-led hospital care, and spells of hospital admission and discharge. As HRG codes and costs change over time, all HRG codes were converted to the 2016–17 National Tariff[25] (Table S1 in the Supporting Information). This was accomplished by attaching a full description of the HRG name or procedure to each code to ensure they matched and corresponded to the same procedure across the years. Costs associated with patients' hospital stays were calculated by continuous inpatient spell, HRG code and trim day, with the latter taking into consideration the number of days each patient spent in hospital below (inlier bed days) and above (excess bed days) the trim point.

2.7 | Cost analysis

The total cost per patient was calculated by summing the cost of prescribed iron preparations, the cost of blood tests, GP consultations and hospital stays. A cost multiplier was introduced, such that the cost of "new iron" could range between 1 (= cost of standard iron salts) and 10 times the cost of existing oral iron preparations.

Given the large sample size, the central limit theorem was assumed to apply, and health state costs were obtained from the coefficients of variables included in a linear (ordinary least squares) regression, specified with total costs as the dependent variable, health states and time on treatment (in days) as explanatory variables:

$$C_T = \sum_{i=1}^{i=6} \beta_i X_i + \beta_7 \cdot \text{TimeOnTreatment} + \epsilon$$

where X = health state and ε is the error term.

2.8 | Base-case analysis

Treatments received by patients in the CPRD sample were assumed to reflect standard care; while the simulated effect of the intervention (in the base-case analysis) considered the hypothetical, new iron preparation only for those who resided in the treatment-intolerant health states.

TABLE 2 Unit cost of iron preparations, general practitioner consultations and phlebotomy

Item of resource use	Unit cost (£)	Reference
Medicines (per pack of 28)		
Fefol Spansules (Intrapharm Laboratories Ltd)	4.25	17
Feospan 150 mg Spansules (Intrapharm Laboratories Ltd)	4.25	17
Ferrograd 325 mg modified-release tablets (Teofarma)	2.58	17
Ferrograd C modified-release tablets (Teofarma)	3.20	17
Ferrograd folic 325 mg/350 μg modified-release tablets (Teofarma)	2.64	17
Ferrous fumarate 140 mg/5 mL oral solution	3.73	17
Ferrous fumarate 140 mg/5 mL oral solution sugar free	3.73	17
Ferrous fumarate 210 mg tablets	3.50	17
Ferrous fumarate 305 mg/folic acid 350 μg capsules	2.33	17
Ferrous fumarate 305 mg capsules	2.33	17
Ferrous fumarate 322 mg/folic acid 350 μg tablets	1.00	17
Ferrous fumarate 322 mg tablets	1.00	17
Ferrous gluconate 300 mg tablets	2.61	17
Ferrous sulfate 150 mg/folic acid 500 μg modified-release capsules	3.95	17
Ferrous sulfate 150 mg modified-release capsules	3.95	17
Ferrous sulfate 160 mg modified-release tablets	3.95	17
Ferrous sulfate 200 mg tablets	2.23	17
Ferrous sulfate 200 mg tablets (A A H Pharmaceuticals Ltd)	2.78	17
Ferrous sulfate 200 mg tablets (IVAX Pharmaceuticals UK Ltd)	2.78	17
Ferrous sulfate 325 mg/ascorbic acid 500 mg modified-release tablets	3.20	17
Ferrous sulfate 325 mg/folic acid 350 μg modified-release tablets	2.64	17
Ferrous sulfate 325 mg modified-release tablets	2.58	17
Fersaday 322 mg tablets (Mercury Pharma Group Ltd)	1.00	17
Fersamal 140 mg/5 mL oral solution (Forley Generics Ltd)	3.73	17
Fersamal 210 mg tablet (Forley Generics Ltd)	3.50	17
Fersamal 210 mg tablets (Mercury Pharma Group Ltd)	3.50	17
Galfer 305 mg capsules (Thornton & Ross Ltd)	2.33	17
Galfer FA capsules (Thornton & Ross Ltd)	2.33	17
Pregaday 322 mg/350 μg tablets (Focus Pharmaceuticals Ltd)	1.25	17
General practitioner consultation (per visit)	45.00	18
Phlebotomy (HRG DAPS08) (per test)	3.37	19

Given the analysis is based on a hypothetical intervention, a threshold analysis was performed to identify the value-based prices at which a "new iron" therapy is cost-effective at £20 000 per QALY gained, by varying the cost of "new iron" (as a multiplier of the mean cost of existing iron products) for two different probabilities of reduction in treatment intolerance (30% and 40%). The base-case analysis therefore established the value-based price of "new iron" which satisfies:

$$\text{Costs}_{(\text{New\_Iron})} = \lambda \cdot \left(\text{QALY}_{(\text{New\_Iron})} - \text{QALY}_{(\text{Standard\_Care})}\right) + \text{Costs}_{(\text{Standard\_Care})}$$

where $\text{Costs}_{(\text{New\_Iron})}$ and $\text{Costs}_{(\text{Standard\_Care})}$ are the total costs to the NHS associated with new and standard iron preparations, respectively; and $\text{QALY}_{(\text{New\_Iron})}$ and $\text{QALY}_{(\text{Standard\_Care})}$ are the expected QALYs for the intervention and control groups. λ is the cost-effectiveness threshold of £20 000 per QALY.

2.9 | Sensitivity analysis

One-way sensitivity analyses were conducted to assess the impact of varying each health state utility by ± 0.1 on value-based prices under the base-case scenario of 30% and 40% reduction in the probabilities of treatment intolerance. These were depicted as tornado plots. The health utility corresponding to the state of anaemia being resolved was not varied as this was based on population norms.

A two-way sensitivity analysis was performed to estimate the incremental cost-effectiveness ratio (ICER) for "new iron" versus standard treatment for different combinations of prices of "new iron" and probability of being treatment intolerant.

The improved safety of "new iron" was modelled as reductions in the relative risk of being treatment intolerant (in 5% increments up to 50%) and higher probabilities of being in corresponding treatment-tolerant states. For instance, a 5% relative decrease in the probability of being in the "*improvement & intolerant*" health state required a corresponding increase in the probability of "*improvement & tolerant*". Similar changes were modelled for the "*no improvement & tolerant*" and "*no improvement & tolerant*" health states. In order for probabilities to sum to 1, they were normalised by sharing any small residual difference across the six health states.

Threshold analyses were undertaken to test the sensitivity of the value-based price, assuming a 30% and 40% decrease in the probability of treatment intolerance, to changes in health state utilities, costs and transition probabilities.

2.10 | Probabilistic sensitivity analyses

A probabilistic sensitivity analysis was performed to consider the joint uncertainty in costs and QALYs. Correlation between cost parameters in the regression model was preserved using the Cholesky decomposition of the variance–covariance matrix. Monte Carlo simulation was conducted to obtain 10 000 correlated draws from a multivariate normal distribution.[26] For utilities, a fixed standard deviation of 0.2 was assumed, and 10 000 draws made from independent beta distributions fitted using the method of moments. Cost-effectiveness acceptability curves were constructed for two combinations each of the price of "new iron" (5 and 10 times the price of iron salts) and the probability of treatment intolerance (reduced by 30% and 40%).[27]

2.11 | Scenario analysis

A scenario analysis was conducted to estimate the ICERs for "new iron" versus standard treatment for different prices of "new iron" and reduced probabilities of being treatment intolerant in the "*hospitalisation*" health states in addition to the "*no improvement & intolerant*" and "*improvement & intolerant*" states. As described above, the probability of treatment tolerance was increased in the opposite correspondent health states "*no improvement & tolerant*", "*improvement & tolerant*" and "*anaemia resolution*". Probabilities were again normalised to sum to 1 by distributing small differences equally across the six health states.

All analyses were conducted using Stata version 13 (StataCorp 2013), Microsoft Excel (2016) and RStudio. The reporting of the economic analysis is compliant with the Consolidated Health Economic Evaluation Reporting Standards.[28]

3 | RESULTS

3.1 | Resource use and costs

Patients residing in the "*no improvement & intolerant*"; and "*no improvement & tolerant*" states recorded the highest mean number of GP visits, at 1.08 and 1.03 per 60-day period, respectively, with associated mean costs of £48.74 and £46.40. Patients in the "*improvement & tolerant*" and "*improvement & intolerant*" health states recorded 0.99 and 0.94 GP visits per 60-day period, costing £44.37 and £42.21, respectively. The "*anaemia resolved*" health state saw the lowest number of GP visits, at 0.21 with an associated mean cost of £9.63.

Iron supplements were prescribed more frequently to patients residing in the "*no improvement & intolerant*" and *Hospitalisation* health states with an average of 74.8 and 67.6 doses over the 60-day interval, respectively, at a mean cost of £7.79 and £7.40. Patients in the "*improvement & intolerant*" health state were prescribed 61.7 doses (at a cost of £6.51); while those in the "*no improvement & tolerant*" state 57.9 doses (£5.97), those in the "*improvement & tolerant*" state 56.8 doses (£6.20), and those in "*anaemia resolved*", 28 doses (£3.06). Considering patients' time within, and distribution among, each health state, the mean 1-year cost of iron preparations was £16.55.

The results of the regression analysis indicated that highest total costs were associated with patients who had hospital episodes, reporting a mean 60-day cost of £279.52 (95% CI £257.81–£301.48), while the least costly health state was "*anaemia resolved*" at £80.00 (95% CI £46.87–£113.58) (Table 3).

TABLE 3 Health state utilities and 60-day costs

	Description	Utility (SD)	Cost (£) (95% CI)
State 1	No improvement in Hb (<2 g/dL), tolerant to treatment	0.76 (0.2)	141.51 (119.19, 164.00)
State 2	Improvement in Hb (≥2 g/dL), tolerant to treatment	0.85 (0.2)	130.07 (108.34, 152.12)
State 3	No improvement in Hb (<2 g/dL), intolerant to treatment	0.72 (0.2)	146.68 (125.28, 168.49)
State 4	Improvement in Hb (≥2 g/dL), intolerant to treatment	0.76 (0.2)	165.64 (144.13, 1187.46)
State 5	Anaemia-related hospital admission	0.72 (0.2)	279.52 (257.81, 301.48)
State 6	Resolution (Hb ≥ 12 g/dL)	0.90 (0.2)	80.00 (46.87, 113.58)

3.2 | Incremental analysis and value-based pricing

The model reflecting current use of iron salts yielded a mean total cost to the NHS of £779.24 over 1 year, and 0.839 QALYs. Assumed 30% and 40% relative risk reductions in the likelihood of treatment intolerance with "new iron" resulted in 0.0064 and 0.0086 QALY gains in comparison with iron salts (Table 4). Threshold analyses indicated that at the £20 000 per QALY threshold willingness to pay, the price of "new iron" could increase to 7.30 and 9.44 times that of the basket of iron salts (£1.38 per 28 tablets) to remain cost-effective with 30% and 40% reductions in treatment intolerance. This is equivalent to £10.07 and £13.02 per 28 tablets (Figure 2). At the higher threshold of £30 000 per QALY, the value-based prices of "new iron" are 10.20 and 13.33 times the price of iron preparations (equivalent to £14.07 and £18.38 per 28 tablets) for 30% and 40% relative risk reductions in intolerance, respectively.

3.3 | Sensitivity analyses

The one-way sensitivity analyses indicated that the value-based price was most sensitive to utility values in the state of "*improvement & tolerant*" (Figure 3). An increase in utility by 0.1 resulted in higher value-based prices of £27.60 and £31.05 for the scenarios of the "new iron" reducing the risk of intolerance by 30% and 40%, respectively. However, a decrease in utility by 0.1 in three health states led to negative value-based prices, reflecting the fact that the "new iron" would be in the south-west quadrant of the cost-effectiveness plane.

TABLE 4 Two-way sensitivity analysis, presenting the incremental QALYs and incremental costs

% reduction in intolerance	Incremental QALYs	Cost of "new iron" relative to the average cost of current iron preparations									
		x1	x2	x3	x4	x5	x6	x7	x8	x9	x10
-5%	0.0010	−2.81	20.28	42.37	64.46	86.55	108.64	130.73	152.82	165.91	197.00
−10%	0.0021	−3.63	18.47	40.56	62.65	84.74	106.83	128.92	151.01	173.10	195.20
−15%	0.0031	−5.45	16.64	38.73	60.83	82.92	105.01	127.10	149.20	171.29	193.38
−20%	0.0042	−7.29	14.81	36.90	58.99	81.09	103.18	125.28	147.37	169.47	191.56
−25%	0.0053	−9.13	12.96	35.06	57.15	79.25	101.34	123.44	145.54	167.63	189.73
−30%	0.0064	−10.99	11.11	33.21	55.30	77.40	99.50	121.59	143.70	165.79	187.89
−35%	0.0075	−12.85	9.25	31.34	53.44	75.54	97.64	119.74	141.84	163.94	186.03
−40%	0.0086	−14.73	7.37	29.47	51.57	73.67	95.77	117.87	139.97	162.07	184.17
−45%	0.0097	−16.62	5.49	27.59	49.69	71.79	93.89	116.00	138.10	160.20	182.30
−50%	0.0108	−18.50	3.59	25.70	47.80	69.90	92.01	114.11	136.21	158.32	180.42

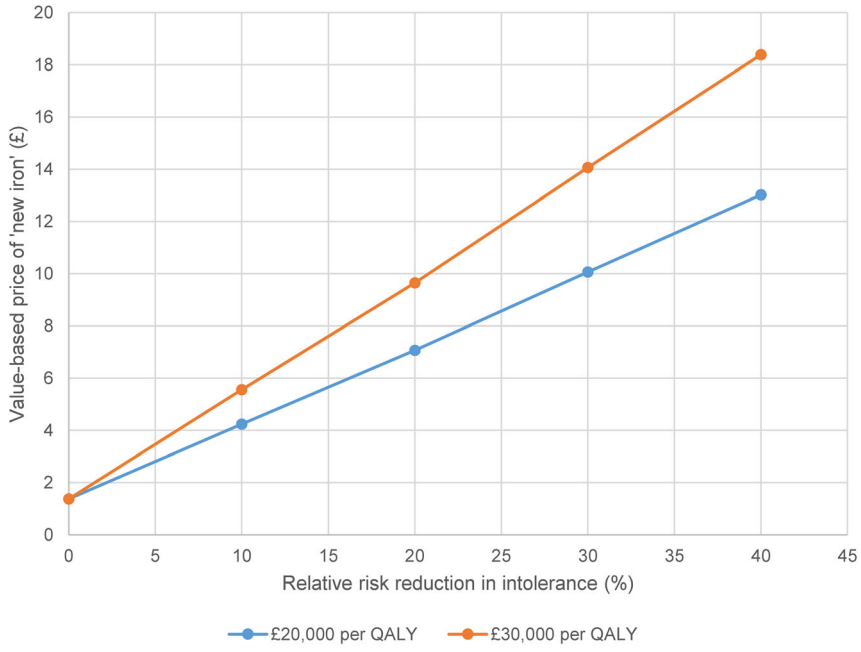
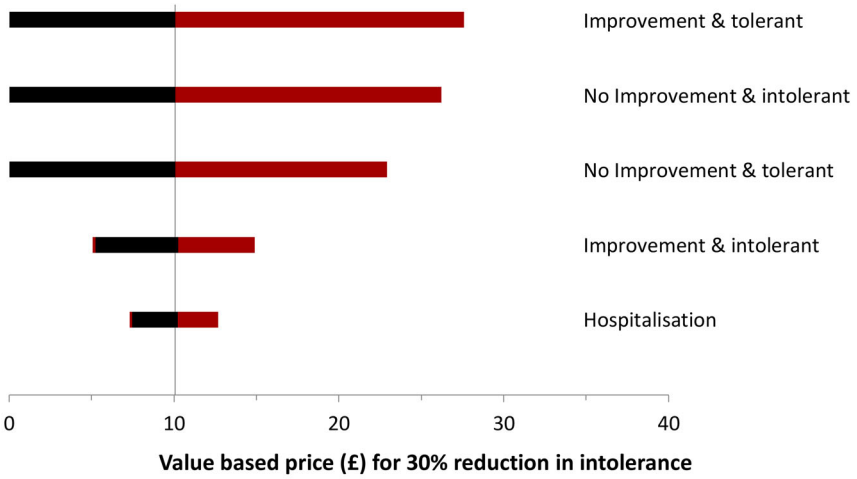


FIGURE 2 Value-based price (£ per 28 tablets) of a hypothetical new oral iron preparation, according to different relative reductions in the probability of treatment intolerance, and for the upper and lower bounds of the willingness to pay threshold range



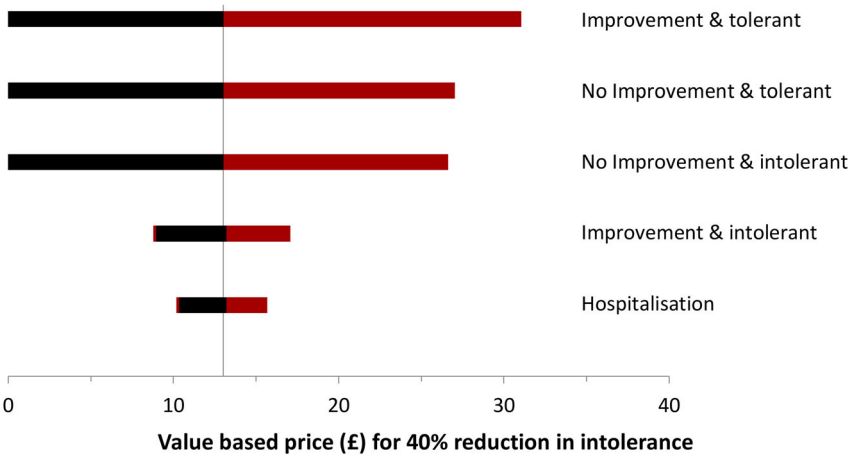


FIGURE 3 Tornado plots depicting the sensitivity of the value-based price (£ per 28 tablets) to changes in health state utility (± 0.1). Vertical lines indicate the base-case value-based prices at 30% (upper figure) and 40% (lower figure) reduction in intolerance

TABLE 5 Two-way sensitivity analysis for the base-case, illustrating the dependency of the incremental cost-effectiveness ratio on the price of "new iron" and effectiveness in terms of reduction in intolerance

% reduction in intolerance	Cost of "new iron" relative to the average cost of current iron preparations									
	x1	x2	x3	x4	x5	x6	x7	x8	x9	x10
−5%	−1790	20 074	41 938	63 802	85 665	107 530	129 394	151 257	164 213	194 985
−10%	−1718	8750	19 218	29 686	40 154	50 623	61 091	71 559	82 027	92 495
−15%	−1753	5350	12 453	19 556	26 659	33 762	40 865	47 968	55 071	62 174
−20%	−1731	3517	8764	14 012	19 260	24 507	29 755	35 002	40 250	45 497
−25%	−1720	2441	6602	10 763	14 924	19 084	23 245	27 406	31 567	35 728
−30%	−1714	1733	5180	8627	12 074	15 521	18 968	22 416	25 863	29 310
−35%	−1712	1231	4173	7116	10 058	13 001	15 943	18 886	21 828	24 770
−40%	−1711	856	3423	5989	8556	11 123	13 690	16 256	18 823	21 390
−45%	−1711	565	2841	5117	7393	9670	11 946	14 222	16 498	18 774
−50%	−1712	332	2377	4422	6466	8511	10 556	12 600	14 645	16 690

Cells shaded in green indicate incremental cost-effectiveness ratios (£/QALY gained; ICERs) that are below the £20 000 per QALY threshold; amber indicates £20 000 to £30 000 per QALY; and red ≥£30 000 per QALY. Negative ICERs indicate incremental QALY gains and cost savings.

The two-way analysis (Table 5) indicates zones of cost-effectiveness and ineffectiveness for different combinations of reductions in treatment intolerance and the cost of "new iron" relative to current oral iron salts. With the exception of the scenario of price parity and reduced intolerance, where "new iron" would be expected to be, the ICERs indicated that higher prices

may be set for "new iron" treatments with lower probabilities of intolerance.

The results from the probabilistic sensitivity analysis, assuming "new iron" is priced at 5 times the average cost of iron salts, and associated with 40% reduced probability of treatment intolerance, indicated that "new iron" is likely to be cost-effective, with 0.94 and 0.98 probabilities of being cost effective at willingness to pay thresholds of £20 000 and £30 000 per QALY, respectively (Figure S1 in the Supporting Information). At 10 times the cost of iron salts, and 30% relative reduction in intolerance, the probability of "new iron" being cost effective reduces to 0.21 and 0.65 for willingness to pay values of £20 000 and £30 000 per QALY, respectively.

3.4 | Scenario analysis

In the alternative scenario where "new iron" is assumed not only to reduce the probability of treatment intolerance, but also the probability of residing in the hospitalisation health state, there were more zones of cost-effectiveness for the same combination of reduction in intolerance and prices of "new iron" (Table S2 in the Supporting Information).

4 | DISCUSSION

Oral iron supplements are among the most frequently prescribed medicines in primary care.[3] Patients who experience ADRs, and are therefore unable to tolerate treatment, may benefit from alternative forms of oral iron, including non-iron salt supplements that are available or currently in development. The determination of value-based prices provides a basis for assessing commercial viability for developers of new treatments, while also assisting the NHS in its horizon scanning activities.

This analysis estimated that for new iron preparations that reduce the relative risk of ADRs by 30–40%, the value-based price is in the region of £10 and £13 per 28 tablets, or about 7–9 times the price of present-day iron supplementation. At a modest price increase (5-fold), there is a high probability (>90%) of a new iron preparation being cost-effective if able to reduce the risk of treatment intolerance by 40%. However, there is considerable uncertainty over the extent to which new iron treatments might reduce gastrointestinal ADRs. Indeed, there are no head-to-head data of "new iron" formulations versus ferrous salts that enable unbiased comparison of clinical and cost-effectiveness. The value-based price reduces to between £4.24 and £7.07 per 28 tablets for reductions of 10–20% in ADRs.

Notwithstanding, these considerations are timely. In patients with complex iron deficiency anaemia, such as in inflammatory bowel disease, there has been a push towards treatment with intravenous iron therapy.[29] This is because anaemia of chronic disease, which often co-exists with iron deficiency anaemia, can lock down mobile iron and result in poor absorption of oral iron. However, there are several advantages to reducing outpatient visits for intravenous iron and even a necessity to do so in the context of COVID-19.[29] Hence, oral iron approaches should be re-visited.[29] This necessitates a better understanding of the value proposition within the complex array of supplemental iron options for hospital patients just as described above for patients in primary healthcare.

Our analysis had strengths in addressing an important economic question in the context of "new iron" and currently prescribed inexpensive, generic formulations of iron salts. Significant increases in the cost of new treatments, beyond the value-based prices estimated here, would impact adversely on the delivery of healthcare owing to the opportunity costs (the marginal benefits forgone as a result of displacing services to fund the new iron therapies would exceed the benefits gained). Even if priced at the threshold, there would be no immediate net benefits to the NHS.[13] The value-based price should therefore be considered as the *maximally* acceptable price.

The analysis benefited from using routine NHS data which provided accurate estimates of health state occupancy and healthcare resource utilisation associated with the management of iron deficiency anaemia. The CPRD includes patient electronic healthcare records (EHR) collected routinely in primary care[30] and is linked to patients' HES data for accurate determination of hospital care.[31] By applying unit cost to items of resource use, the analysis considered the actual costs of primary and secondary care services in the NHS.

There was, however, a limited evidence base relating to health state utilities requiring assumptions that may not be generalisable to the modelled population. Sensitivity analyses indicated that changes in health state utilities within plausible ranges led to variation in value-based prices. Further research on utilities in iron-deficiency anaemia is warranted. The model structure was also limited by the data available from EHR, and there were no randomised controlled trial data on the relationship between dose and ADR,[4] or the effectiveness of sequential courses of treatment. Our analytic time horizon was set to 12 months, which may not adequately capture all costs and consequences, although it is recommended that treatment with elemental iron should be limited to 3 months after iron deficiency is corrected, this being considered sufficient to allow stores to be replenished.[32]

Finally, we note that, currently in the UK, iron can be administered parenterally when oral therapy is unsuccessful, for example if patients cannot tolerate oral iron, or do not take it reliably. Our economic analysis—very conservatively—did not compare new, hypothetical oral iron preparations with parenteral iron, such as ferric carboxymaltose, or iron dextran, sucrose or isomaltoside 1000. This was principally because the CPRD data extraction was limited to patients being prescribed oral iron supplementation. While there are several budget impact analyses of parenteral iron for this clinical indication, there are no economic analyses; had we considered parenteral products, a higher value-based price would likely have resulted.

In conclusion, a significant proportion of patients with iron deficiency anaemia are intolerant to oral iron salt preparations. This increases the risk of non-adherence and treatment failure as well as

impairing patients' health-related quality of life. The prospect of novel oral iron preparations to reduce the incidence of ADRs warrants careful analysis of how they are to be priced in the context of inexpensive alternative generic iron salts. This value-based pricing analysis estimates that new treatments may be cost-effective at prices that are several-fold higher than existing oral iron salts, and which may be attractive for commercial development while proving to be cost-effective to the NHS.

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COMPETING INTERESTS

The authors have no competing interests.

CONTRIBUTORS

G.C., D.I.A.P., R.A.P., J.J.P. and D.A.H. conceived or designed the work; G.C., L.S., Y.C., D.I.A.P., R.A.P. and D.A.H. acquired, analysed or interpreted the data; G.C., L.S., D.I.A.P., R.A.P., J.J.P. and D.A.H. drafted the work or revised it critically for important intellectual content; all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; and have provided final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Clinical Practice Research Datalink. Restrictions apply to the availability of these data, which were used under license for this study.

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REFERENCES

1. Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372(19):1832-1843.
2. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016;387(10021):907-916.
3. National Health Service Digital. Prescription Cost Analysis—England, 2018. https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018. Accessed November 20, 2020.
4. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS ONE*. 2015;10(2):e0117383.
5. Span K, Verhoef JJF, Hunt H, et al. A novel oral iron-complex formulation: encapsulation of hemin in polymeric micelles and its in vitro absorption. *Eur J Pharm Biopharm*. 2016;108:226-234.
6. Koduru P, Abraham BP. The role of ferric carboxymaltose in the treatment of iron deficiency anemia in patients with gastrointestinal disease. *Therap Adv Gastroenterol*. 2016;9(1):76-85.
7. Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, et al. Tolerability of different oral iron supplements: a systematic review. *Curr Med Res Opin*. 2013;29(4):291-303.
8. Abbas AM, Abdelbadee SA, Alanwar A, Mostafa S. Efficacy of ferrous bis-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. *J Matern Fetal Neonatal Med*. 2019;32(24):4139-4145.
9. Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. *Adv Chronic Kidney Dis*. 2019;26(4):272-291.
10. Mosha TC, Laswai HH, Assey J, Bennink MR. Efficacy of a low-dose ferric-EDTA in reducing iron deficiency anaemia among underfive children living in malaria-holoendemic district of Mvomero, Tanzania. *Tanzan J Health Res*. 2014;16(2):70-78.
11. Pereira DIA, Mohammed NI, Ofordile O, et al. A novel nano-iron supplement to safely combat iron deficiency and anaemia in young children: the IHAT-GUT double-blind, randomised, placebo-controlled trial protocol. *Gates Open Res*. 2018;2:48.
12. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9. Accessed November 20, 2020.
13. Hughes DA. Value-based pricing: incentive for innovation or zero net benefit? *Pharmacoeconomics*. 2011;29(9):731-735.
14. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.
15. National Health Service Digital. Prescription Cost Analysis—England. 2012. https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2012. Accessed November 20, 2020.
16. Su L, Cheng Y, Pereira DIA, Powell JJ. Modelling disease progression with multi-level electronic health records data and informative observation times: an application to treating iron deficiency anaemia in primary care of the UK. 2021. https://arxiv.org/abs/2107.13956. Accessed September 2, 2021.
17. Peuranpää P, Heliövaara-Peippo S, Fraser I, Paavonen J, Hurskainen R. Effects of anemia and iron deficiency on quality of life in women with heavy menstrual bleeding. *Acta Obstet Gynecol Scand*. 2014;93(7):654-660.
18. Ford DC, Dahl NV, Strauss WE, et al. Ferumoxytol versus placebo in iron deficiency anemia: efficacy, safety, and quality of life in patients with gastrointestinal disorders. *Clin Exp Gastroenterol*. 2016;9:151-162.
19. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health*. 2008;11(7):1131-1143.
20. Rohatgi A. WebPlotDigitizer. http://arohatgi.info/WebPlotDigitizer/. Accessed November 20, 2020.
21. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011;31(6):800-804.
22. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. 1999. http://econpapers.repec.org/paper/chyrespap/172chedp.htm. Accessed March 24, 2017.
23. Joint Formulary Committee. *British National Formulary*. 71st ed. London: BMJ Group and Pharmaceutical Press; 2016.
24. Curtis L, Burns A. Unit Costs of Health and Social Care. In: *Personal Social Services Research Unit*. Canterbury: University of Kent; 2016

http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. Accessed November 20, 2020.
25. Department of Health and Social Care. NHS reference costs 2014 to 2015. https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed November 20, 2020.
26. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2011.
27. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ*. 2004;13(5):405-415.
28. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Eur J Health Econ*. 2013;14(3):367-372.
29. D'Amico F, Peyrin-Biroulet L, Danese S. Oral iron for IBD patients: lessons learned at time of COVID-19 pandemic. *J Clin Med*. 2020; 9(5):1536.
30. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. 2019; 48(6). 1740-1740g
31. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. *Eur J Epidemiol*. 2019;34(1): 91-99.
32. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. *Gut*. 2011;60(10):1309-1316.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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